Prevalence of non-communicable diseases in adults living with Human Immunodeficiency Virus. An Overview of Systematic Reviews.

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Thesis presented in fulfilment of the requirements for the degree of Master of Science in Clinical Epidemiology in the Faculty of Medicine and Health Sciences at Stellenbosch University

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April 2019

Declaration

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April 2019

Abstract

Background

Non-communicable diseases (NCD's) are on the rise in patients with HIV and this has been partly attributed to the increasing use of Antiretroviral therapy (ART). Our aim was to consolidate findings on prevalence of NCD in those with HIV, from systematic reviews, to inform the existing body of research and provide evidence to inform planning of healthcare services.

Methods

We undertook a comprehensive search in February 2018, with no date limitations, in 7 databases to identify systematic reviews on the prevalence of NCD's in HIV patients on ART. We included systematic reviews with participants over the age of 13years who were on ART and had one or more of the specified NCD's including diabetes mellitus type 2, hypertension, dyslipidemia and depression. We then assessed the quality of these systematic reviews using the AMSTAR 2 tool and extracted prevalence's of the NCD's from each one of them.

Results

We identified 10 systematic reviews meeting our inclusion criteria of which 3 are ongoing. The methodological quality of the seven systematic reviews assessed varied in many aspects. Only one systematic review assessed prevalence of multi-morbidity defined as the presence of two or more NCD's in people living with HIV (PLHIV) which ranged from 8.4% to 47%, the remaining six only assessed the prevalence of comorbidity of any one NCD in PLHIV. Diabetes mellitus type 2 had the lowest prevalence especially in African countries and it ranged between 7% to 48.6% globally while dyslipidemia had the highest prevalence globally ranging from 6.3% to 100%. Depression in PLHIV who were on ART was considerably high

ranging from 25.81% to 64% while hypertension ranged from as low as 4.0% to as high as 67.0%.

Conclusions

This overview highlights that NCD's are highly prevalent in PLHIV on ART. There is a lack of systematic reviews and primary studies focusing on multi-morbidity in the HIV population on ART.

PROSPERO registration number - CRD42018104420

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Part A: Completed manuscript following requirements as set out in the Instructions for authors of the BMC – Systematic Reviews journal

Keywords

Prevalence

Non-communicable diseases

People living with HIV

Human immunodeficiency virus

Antiretroviral Therapy

Background

The global prevalence of human immunodeficiency virus (HIV) has increased from 33.3 million people in 2010 to 36.7 million people approximately by the end of 2015. Over the years, the use of combined Antiretroviral Therapy (ART) has reduced mortality from acquired immunodeficiency syndrome (AIDS). Deaths from AIDS reduced from 1.5 million in 2010 to 1.1 million by the end of 2015. Also, life expectancy has increased due to the several mechanisms through which ART suppress viral replication, reduce the occurrence of opportunistic infections and improve immune function. It has been documented that the use of ART has led to a stability in the acquisition of new HIV infections amongst all ages. The number of new infections dropped by a million people from 2.2 to 2.1 million in 2010 and 2015 respectively (1). This may aid the United Nations Program on HIV and AIDS (UNAIDS) to achieve their 90-90-90 goal of ending the AIDS epidemic.

However, with increased life expectancy, aging is inevitable and thus the diseases associated with aging such as cardiovascular abnormalities, hypertension, insulin resistance/diabetes mellitus, cholesterol abnormalities, neurodegenerative disorders and so forth occur. Research suggests the emergence of such diseases much earlier in the HIV population than seen in the general population (2)(3). For instance a cross-sectional study done in the United States (US) in 2010 showed that older HIV patients had a higher prevalence of hypertension 54%, hypertriglyceridemia 51% and low bone mineral density 39% compared to the general population of the same age 38%, 33% and 0% respectively (4). Another cross-sectional study done in Brazil suggested that there is premature aging in people living with HIV (PLHIV) by 15 years and that HIV is diagnosed at an early age between 18-39years (5) leading to increased ART use in the older population and increasing the incidence of non-communicable diseases (NCD's) such as hypertension, dyslipidemia, diabetes mellitus, obesity and depression with older age (5), (6), (7) due to prolonged exposure to ART.

Aging is not the only mechanism leading to the development of NCD's, these findings can be attributed to the disease process itself via its viral properties or the inflammation and reaction by the human body, and to the toxic effects of the ART which lead to ART induced endothelial dysfunction as shown by a systematic review done by Nduka CU et al (8). Also, studies reveal that the number of years since the diagnosis of HIV and the duration and type of ART received is crucial in the development of NCD's. A cross-sectional study done in Mwanza region of Tanzania in 2013 showed that PLHIV on ART for more than 2 years had a prevalence of 28.7% for hypertension while those naïve to ART had a prevalence of 5.3% (9).

Another important aspect of ART is the type of ART in question, it has been shown that people receiving a combination of Zidovudine/Lamivudine/Nevirapine (1st line treatment) are at an increased risk of hypertension while those receiving the non-standard 1st line treatment or the 2nd line drugs are at increased risk of Diabetes (10). Long duration of ART and usage of protease inhibitors have been associated with an increased risk of metabolic syndrome (11).

Because of the slow progress in the decline of new HIV infections amongst adults (12), it has become a chronic problem and is being more associated with NCD's at younger ages than in the general population. A huge burden of HIV of about 71% lies in the Sub-Saharan Africa (SSA) which is home to only about 12% of the global population (13) with marked ART coverage over the last few years in different countries (12) as we aim to reach the 90-90-90 target set by the UNAIDS thus putting patients at the risk of developing NCD's earlier indefinitely.

Models which integrate NCD's within the HIV setting have been identified which include screening for HIV along with NCD's in the general population, screening for NCD's or its

risk factors in HIV patients attending HIV care, integration HIV and NCD care in clinics where patients have both of the conditions, differentiated care for patients who have HIV and/or NCD and integrated healthcare for all patients providing benefits of nutrition and so forth which affects HIV/NCD outcomes(14)(15)(16). However, because HIV linked to NCD is a relatively new concept, integration of screening for risk factors/existing NCD's and its treatment is challenging due to inefficient evidence, lack of funding and poor capacity to support such models of care due to the different disease priorities set by different nations (17)(18)(19). There have been many systematic reviews done on the prevalence of comorbidities in patients with HIV with varying results in different populations (20)(21)(22) For instance the prevalence of diabetes mellitus was found to be the lowest in most systematic reviews while hypertension and cardiovascular diseases were more prevalent with broader range of values (22)(23). However, we cannot ascertain the quality of evidence for these systematic reviews. Hence our aim was to consolidate all the available findings to summarize the global prevalence of co- and multi-morbidity with one or more NCD's namely diabetes mellitus type 2, hypertension, dyslipidemia and depression in adults with HIV on ART in order to provide information to health institutions for planning and integration of healthcare services. Also, new primary studies need to be informed by the existing body of research.

Methods

This is an overview of systematic reviews summarizing information from multiple systematic reviews following general principles using the Cochrane handbook version 5.1.0.

The protocol for this study was registered in PROSPERO with the registration number CRD42018104420.

Selection Criteria

We included systematic reviews conducted globally comprising of primary studies from any region in the world which assessed the prevalence of NCD's using cross-sectional study designs in adults with HIV who were on treatment with any regimen of ART and excluded systematic reviews in which pregnant women were the study population. Cross-sectional studies in which groups of participants were being compared for the prevalence of NCD's were included only if the said group comprised of participants who were on ART. We also reviewed the protocols of ongoing systematic reviews that meet our inclusion criteria and will include their results in this overview if they are completed prior to publishing it. Systematic reviews are defined as studies that answer a research question by collecting and summarizing all empirical evidence that fits pre-specified eligibility criteria. It must have its objectives stated a priori and should have searched for studies on two or more databases including grey literature/unpublished work. Extracted data should have been analyzed, and a risk of bias assessed for each study with results presented appropriately (24).

Our primary outcome was to assess the prevalence of multi morbidity with diabetes mellitus type 2, hypertension, dyslipidemia and depression in adults with HIV on ART while the secondary outcomes of our study were to assess the prevalence of co morbidity with any of the above mentioned NCD's in adults with HIV on ART; and, to identify the distribution of these NCD's according to demographics such as age, gender, duration and type of ART.

Definitions

Multi morbidity is defined as the existence of two or more chronic medical conditions in a person that reduces his quality of life and functional abilities leading to increased hospital visits (25). The presence of HIV along with two or more NCD's is described as multi

morbidity while the presence of one chronic disease in a patient with HIV is described as comorbidity in this systematic review.

Diabetes mellitus type 2 is a chronic disease which is characterized by hyperglycemia due to the body's inability to effectively utilize insulin, and, uncontrolled diabetes over time may lead to severe damage especially to the nerves and blood vessels. The diagnosis of diabetes is made by doing fasting blood glucose (FBG) > 7mmol/L, random blood glucose of > 11.1mmol/L, glycated hemoglobin (HbA1c) > 6.5mmol/L or a two hour oral glucose tolerance test (OGTT) of > 11.1mmol/L (26).

Hypertension is defined as persistently raised systolic and/or diastolic blood pressures of >140mmHg and >90mmHg respectively. Patients with raised blood pressures or identified using any antihypertensive medications are diagnosed to be hypertensive (27).

Depression is part of a range of depressive disorders which are characterized by the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5^{TM}) has grouped the following under depressive disorders: disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder (28).

Dyslipidemia is defined as elevated total serum cholesterol of > 5mmol/L or elevated low density lipoproteins (LDL) of > 3mmol/L or raised Triglycerides > 1.7mmol/L or low levels of high density lipoproteins (HDL) < 1.2mmol/L. Measuring the lipid profile or self-reported use of lipid lowering drugs by the patients can be used to confirm the diagnosis (29).

Search Strategy

With assistance from an information specialist, we conducted a search for existing systematic reviews in 7 databases including the MEDLINE, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and EBSCOHost, Web of Science, Epistemonikos and, in PROSPERO to identify any ongoing systematic reviews. We did not apply any restrictions to date, language or publication status in our search. However, we did not further look for systematic reviews from other sources such as reports nor contacted any specialists. Terms that we used to inform our search included those for non-communicable diseases, HIV, ART, systematic reviews, Type 2 diabetes mellitus, Hypertension, Depression, and Dyslipidemia (Additional file 1).

Selection of systematic reviews

Two authors (SJ and TY) independently assessed the eligibility of the articles obtained from the electronic search by screening through their titles and abstracts to determine potentially eligible systematic reviews. We then obtained full texts for screening and applied the pre-specified eligibility criteria in order to include these systematic reviews in our overview. Any discrepancy in the selection of studies was resolved by discussion between the two authors.

Data extraction and management

One author (SJ) extracted data from the included systematic reviews into a predesigned and piloted data extraction form. The second author (TY) checked the data that were extracted which included:

- Characteristics of the systematic reviews including their study designs, when was it conducted, how many primary and specifically cross-sectional studies did it include, where have the cross-sectional studies been conducted and what its objectives are.
- Participants' characteristics including age groups, gender and types/classes of ART's being used.
- Results of the reviews i.e. the prevalence of each type of NCD assessed and the prevalence of two or more NCD's in PLHIV.

We summarized data from each systematic review in the table of characteristics of included systematic reviews (Tables 1 and 2) and also did a mapping of cross-sectional studies from each systematic review (Table 3) to identify an overlap of cross-sectional studies between the systematic reviews.

Assessment of methodological quality of included systematic reviews

We assessed the methodological quality of each of the included systematic reviews using the AMSTAR 2 tool (30) which is a revision of the AMSTAR tool in order to identify high quality systematic reviews. AMSTAR 2 is a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of health care interventions. It consists of 16 domains which must be answered with a yes, partial yes or a no (30). Not all the domains of the AMSTAR 2 tool have been addressed because some of them are only applicable to intervention studies. Hence, we only answered questions in the domains that are pertinent to appraising the quality of systematic reviews in general. We did not generate an overall score for each of the included systematic review, but rather considered the potential impact of an inadequate rating for each item.

We resolved discrepancies in the data extracted from the systematic reviews by obtaining the cross-sectional study which was included in the systematic review and reviewing its findings. Disagreements between the two authors (SJ and TY) were solved by discussion with each other.

Data analysis

Because of the nature of the primary studies involved we provide a narrative summary of our findings considering all the participants, their NCD and ART status. We report on the prevalence of each type of NCD identified as well as the prevalence of two or more NCD's in PLHIV with its 95% confidence interval as reported in the included systematic reviews.

Results

Description of included systematic reviews

Our search yielded a total of 1600 articles (Figure 1) and after deduplication and screening, we remained with 10 systematic reviews for inclusion in this overview. The major reasons for excluding articles include systematic reviews which did not assess the prevalence of NCD's using cross-sectional study designs instead they measured incidence/association and included other primary study designs, or their participants were not on ART or they included children and pregnant women (Table 4). Because of the different cut offs used for age within the included systematic reviews, we included participants from the age of 13 years onwards. Most of the systematic reviews that we have included comprise of HIV participants who were on ART and those who were ART naïve, hence, we have only considered the results of those in the ART group.

In this overview, the included systematic reviews were conducted between 2009 and 2017. Seven out of the 10 systematic reviews which meet our inclusion criteria have been completed. They are included in the Table of complete systematic reviews (Table 1) while 3 of them are ongoing systematic reviews (Table 2). The completed systematic reviews include a combination of observational studies including cohort, case control and cross-sectional study designs hence we have mapped out only cross-sectional studies as per our criteria to observe their overlap within the included systematic reviews.

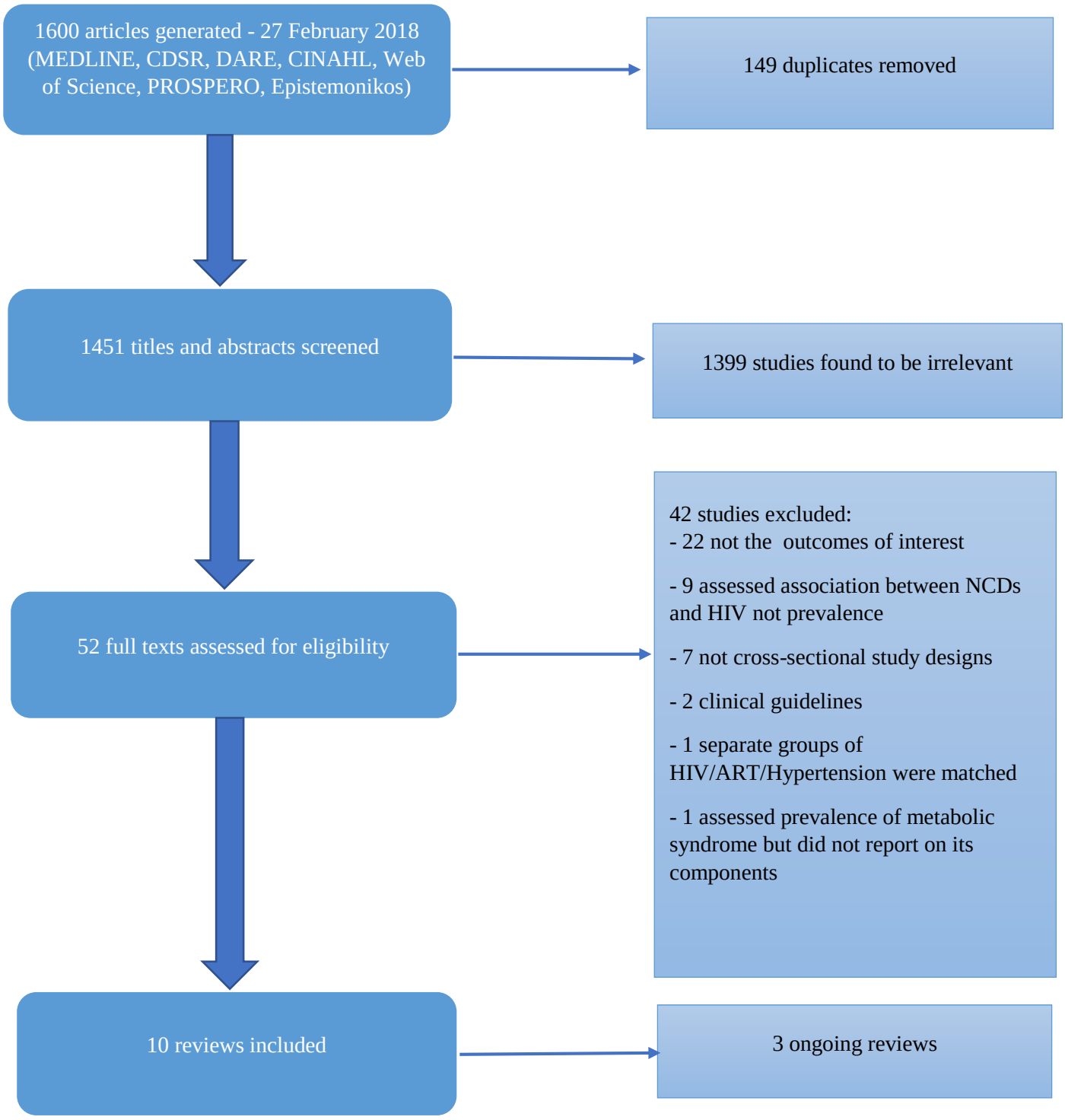

Figure 1 – PRISMA Flow diagram

Table 1: Completed Systematic Reviews

Study ID	Review question	Date of the search	No. of primary studies included	No. of cross-sectional studies within the review	Population description	Prevalence of the type of NCD on ART
Bernard 2017 (31)	Prevalence and factors associated with depression in people living with HIV in Sub-Saharan Africa: A systematic review and meta-analysis	April 2016	66	61	Adults; SSA	Depression
Brandt 2009 (32)	The mental health of people living with HIV/AIDS in Africa: a systematic review	August 2008	24	19	Adults; SSA	Depression
Lowther 2014 (33)	Experience of persistent psychological symptoms and perceived stigma among people with HIV on antiretroviral therapy (ART): A systematic review	August 2013	66	43	Adults and children; HIC and LMIC	Depression
Naidu 2017 (34)	Prevalence of Metabolic Syndrome Among People Living with HIV in Developing Countries: A Systematic Review	April 2015	18	15	Adults; Africa, Asia, South America	Diabetes, Hypertension, Hypertriglyceridemia, low HDL
Nguyen 2015 (35)	Burden, Determinants, and Pharmacological Management of Hypertension in HIV-Positive Patients and Populations: A Systematic Narrative Review	February 2015	101	34	Adults; HIC and LMIC	Hypertension
Prioreschi 2017 (36)	Incidence and prevalence of type 2 diabetes mellitus with HIV infection in Africa: a systematic review and meta- analysis	May 2016	20	13	Adults; Africa	Diabetes
Xu 2017 (37)	Global prevalence of hypertension among people living with HIV: a systematic review and meta-analysis	December 2016	49	36	Adults; America, Africa, Europe, Asia	Hypertension

Table 2: Ongoing Systematic Reviews

Study ID	**Review question**	**Prevalence of the type of NCD on ART**
Bigna 2017 (38)	Prevalence and incidence of hypertension in the global HIV-infected population: a systematic review and meta-analysis protocol	Hypertension
Bigna 2018 (39)	Prevalence and incidence of major depressive disorders among people living with HIV residing in Africa: a systematic review and meta-analysis protocol	Major depressive disorder
Olamide 2016 (39)	Prevalence of metabolic syndrome, discrete or comorbid diabetes and hypertension in sub-Saharan Africa among people living with HIV versus HIV-negative populations: a systematic review and meta-analysis protocol	Diabetes, Hypertension, Hypertriglyceridemia, low HDL

A total of 142 cross-sectional studies (Table 3) are contained within the completed systematic reviews and they have been conducted in 6 continents including Africa, Asia, North America, South America, Europe and Australia with majority of them capturing data from low and middle-income countries (LMIC). African countries in which these cross-sectional studies have been conducted include Ethiopia, Kenya, Malawi, Rwanda, Tanzania, Uganda and Zambia from Eastern Africa, Cameroon and Zaire/Democratic Republic of the Congo from Central Africa, Gambia, Mali, Nigeria and Senegal from Western Africa, And Botswana, Namibia and South Africa from Southern Africa. while the remaining were conducted in Australia, Brazil, Canada, China, Croatia, Ecuador, France, Germany, Hungary, India, Italy, Jamaica, Malaysia, Netherlands, Portugal, Serbia, Spain, Sweden, Taiwan, Thailand, United States and Vietnam.

The initial number of primary studies within the systematic review was 178, however, because some of them involved HIV positive and negative participants and those who were HIV positive were not on ART, or the study design was a survey conducting a census on the population at large with unconfirmed ART status and sub-group information, or some of the primary studies were not cross-sectional studies as mentioned in the review and rather a cohort study design had been employed with no baseline data, we excluded them from this

overview. We also excluded cross-sectional studies for which we could not ascertain the ART status of the participants even after obtaining full texts of the articles. Of note, cross-sectional studies which included 2 arms; one of HIV positive and the other one of HIV negative participants, we retained those studies in which the HIV positive participants were on ART and if the two arms were patients on ART and ART naïve then we also retained them in the table. With regards to the proportion of people on ART in each of these cross-sectional studies, we observed that not all of them were able to find all patients who were on ART and thus the percentage of participants in totality between all the cross-sectional studies ranged from 18% to 100%. However, half of the cross-sectional studies (50%) have reported ART use of 100% in their participants.

We only found one systematic review (Naidu 2017) which included 17 cross-sectional studies, assessing the prevalence of multimorbidity i.e. dyslipidemia, diabetes mellitus type 2 and hypertension in patients with HIV on ART. Cross-sectional studies in this systematic review were conducted in African, Asian and South American countries including Botswana, Cameroon, Ethiopia, South Africa, India, Thailand, Argentina, Brazil, Colombia, Ecuador, Peru and Venezuela. , Of the 6 systematic reviews that assessed the prevalence of co-morbidity,3 of them looked at depression amongst the HIV population,2 assessed the prevalence of hypertension and only 1 sought to look at the burden of diabetes mellitus (Table 1).

We found some amount of overlap of cross-sectional studies between the systematic reviews whereby 28 were included in more than one systematic review. Of note, only the cross-sectional study conducted by Poupard et al (40) are referenced in 3 systematic reviews while 28 of them are referenced in two systematic reviews (Table 3).

Quality of included reviews (AMSTAR)

We assessed the quality of systematic reviews included in this overview using the AMSTAR 2 tool (30). We only used questions pertaining to systematic reviews of cross-sectional studies (11 domains out of 16 were assessed) (Table 5 and Additional file 2). All the systematic reviews had clear research questions in terms of population and outcomes of interest, which then led to a good elaboration of the included cross-sectional studies in terms of the PICOT (population, intervention, comparator, outcome and time frame) elements within their table of included studies. Two systematic reviews (41)(33) did not provide very detailed information in their table of included studies and thus received partial yes scores. None of the systematic reviews provided a table of excluded studies.

All but two of the systematic reviews (35),(36) did not mention anything about developing a protocol with review methods being determined a priori, and only one systematic review (36) provided their protocol registration number while for the other (35) the corresponding author confirmed the existence of a protocol which was not registered. All of the systematic review authors did not search comprehensively as they all scored a partial yes because either they did not search grey literature, reference lists, contacted experts in the field etc. or, only searched in one database. Screening and data extraction were not very clearly described in majority of the systematic reviews as there was uncertainty whether it was done by 2 independent authors. Only one systematic review (36) performed screening and data extraction as per the standards while another (34) screened appropriately however their method of data extraction is not clear. Screening in Lowther (33) and Xu (42) et al was done by one author.

All did not report funding for the cross-sectional studies included in their systematic reviews, however, they all reported on their own funding sources and declared conflicts in their systematic reviews as per the requirements of systematic reviews. All, but one systematic review (36) explored reasons around heterogeneity in their results, and 3 (31),(36),(34) of them went on to do a meta-analysis to show the pooled prevalence's from the primary studies. However, authors that performed meta-analysis in their systematic reviews failed to report on publication bias in their findings and the rest of them did not mention it. In summary, the quality of the evidence base from these systematic reviews would be considered to be of low to moderate as key aspects related to their methods including conducting the search, screening and data extraction etc. are not clearly emphasized on.

Table 5: AMSTAR 2 – Assessment of the quality of included systematic reviews

AMSTAR 2 Criteria	Bernard 2017	Brandt 2009	Lowther 2014	Naidu 2017	Nguyen 2015	Priores-chi 2017	Xu 2017
Did the research questions and inclusion criteria for the review include the components of PICO? Was the research question clear?							
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?							
Did the review authors use a comprehensive literature search strategy?							
Did the review authors perform study selection in duplicate?							
Did the review authors perform data extraction in duplicate?							
Did the review authors provide a list of excluded studies and justify the exclusions?							
Did the review authors describe the included studies in adequate detail?							
Did the review authors report on the sources of funding for the studies included in the review?							
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?							
If they performed quantitative synthesis did the review authors		NA	NA	NA	NA		

carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?							
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?							

Color coding:

Yes = Dark green **Partial Yes** = Light green **No** = Red **Unclear** = Yellow

Prevalence of multi morbidity and comorbidities

Prevalence of multi morbidity in people living with HIV (PLHIV) on ART

We only found one systematic review which assessed the prevalence of multi morbidity in PLHIV (34). Metabolic syndrome (MS) in this study has been defined as the presence of the risk factors which include hypertension, hyperglycemia, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, and abdominal obesity which are associated with an increased risk of cardiovascular disease (CVD) and type II diabetes mellitus when in conjunction (43). They found an overall prevalence of MS in developing countries ranging from 8.4% to 47% with the mean prevalence of MS in South America being 21.4%, that of Asia as 21.5% and the highest in Africa which was 30.5%.

This systematic review included 18 cross-sectional studies of which we excluded one from Table 3 as the study population was ART naïve. The remaining 17 cross-sectional studies included patients that were either all on ART (6 out of 11) or they were grouped as those receiving ART and ART naïve for which comparisons were made between the groups. On comparing the prevalence of MS in patients taking ART and those naïve to ART, only one out of the 8 cross-sectional studies reported a low prevalence of MS in the former group

(19.1% vs 21.7%). Ten of the cross-sectional studies also compared prevalence of MS according to gender and 80% of these reported a higher prevalence of MS in females which ranged from 18.7% to 46.8%. This systematic review further describes the prevalence of each of the components of MS in PLHIV which will be discussed in the section below.

Prevalence of co-morbidity in PLHIV on ART

Depression in PLHIV on ART

We found that the prevalence of depression in PLHIV on ART has been reported by 3 systematic review (41),(33),(31). A total of 77 cross-sectional studies form part of these systematic reviews of which Brandt 2009 only contributes 5 because of reasons explained earlier. Major Depressive Disorders (MDD) in these cross-sectional studies was assessed using the Mini-International Neuropsychiatric Interview (MINI) whereas for depression and depressive symptoms the Beck Depression Inventory (BDI), the CES-D (Centre for Epidemiological Studies depression tool), Hospital Anxiety and Depression scale (HADS), Patient Health Questionnaire (PHQ-9) and the Hopkins Symptom Checklist (HSCL-D) were used.

Lowther et al (33) reports a point prevalence of depression ranging from 25.81% in high income countries to 41.36% in low- and middle-income countries with a mean of 33.6%. Bernard et al (31) on the other hand report on MDD and depressive symptoms. They reported that the prevalence of MDD in PLHIV on ART ranged between 3% to 14.2%. The prevalence of depressive symptoms was assessed for each tool used, some of which were pooled together in a meta-analysis to give a pooled prevalence. The pooled prevalence of depressive symptoms in PLHIV on ART using the CES-D tool found to be 32% with a high between group heterogeneity. Using the PHQ-9 tool the pooled prevalence of depressive symptoms in

PLHIV on ART was found to be 14% with a high between group heterogeneity. The BDI tool gave a high pooled prevalence of 43% with no between group heterogeneity. Using the HSCL tool, the pooled prevalence of depressive symptoms was found to be 13% with a low between group heterogeneity. Brandt 2009 (41) reports a high prevalence of depressive symptoms ranging from 30% to 64% in the African population using the tools described above.

Type 2 Diabetes Mellitus in PLHIV on ART

We only found one systematic review (36) which reported on the prevalence of type 2 Diabetes in PLHIV on ART. This systematic review included 20 primary studies of which 6 cross-sectional studies met our inclusion criteria. Five of these compared HIV patients on ART with ART naïve while one compared HIV positive patients on ART with HIV negative patients. Apart from the WHO diagnostic criteria for diagnosing diabetes type II, other criteria used include American Diabetes Association (ADA), National Cholesterol Education Program (NCEP) and International Diabetes Federation (IDF). Prioreschi et al (36) did not report on the prevalence of type II diabetes mellitus. Instead they calculated a risk ratio (RR) for participants on ART treatment compared to those not on ART which included a total of 5 cross-sectional studies. The pooled RR is 1.38 which is not statistically significant (RR=1.38, 95% CI 0.66 to 2.87, p=0.39).

Naidu et al (34) is the systematic review which reported on MS and its components, hyperglycemia being one of them. The prevalence of hyperglycemia ranged between 7 to 48.6% with a mean prevalence of22.5%. Whilst assessing continent wise, they found that the mean prevalence of hyperglycemia in Africa was 18.1%, South America 21.4% and in 23.4% in Asia. The authors did not provide with a numerical value but reported that 5 out of 7 studies in which they compared patients on ART to ART naïve had higher prevalence's of type II diabetes mellitus.

Dyslipidemia in PLHIV on ART

Naidu et al (34) assessed the prevalence of metabolic syndrome in PLHIV. Low HDL cholesterol and Hypertriglyceridemia are 2 of the components of Metabolic syndrome which fall under the diagnosis of dyslipidemia. They reported that the prevalence of low HDL cholesterol from 16 studies ranged from 6.3% to 100% with a mean of 50.1%. Continent wise, the mean prevalence of low HDL cholesterol was almost equal between South America and Asia (50.1% and 53.2% respectively) while Africa had a lower prevalence of 32.8%. Out of seven studies compared for which they did not provide any numerical data, they found that 5 of them had higher prevalence's of low HDL cholesterol in ART naïve patients.

In the same systematic review (34), the prevalence of hypertriglyceridemia was estimated from 15 studies for which the range is 11.5% to 93.8% with a mean of 45.7%. In ascending order, the prevalence's per continent were found to be 24.9%, 45.8% and 54.4% in Africa, Asia and South America respectively. To determine whether patients who are on ART or who are ART naïve have a higher prevalence of hypertriglyceridemia, 7 studies were compared for which no numerical results are provided and all of them showed that the prevalence of hypertriglyceridemia was higher in the ART group.

Hypertension in PLHIV on ART

We identified 2 systematic reviews (35),(42) which report on the prevalence of hypertension in PLHIV on ART including a total of 43 cross-sectional studies. Hypertension in these systematic reviews is defined as a diagnosis based on raised blood pressures of ≥ 140/90 mmHg; systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or known hypertension as self-reported use of antihypertensive by the patient or from the

medical records. Blood pressure ≥ 130/85 mmHg in a known hypertensive was also a criterion for confirming the diagnosis of hypertension.

Of the systematic reviews, Nguyen et al (35) found that the prevalence of hypertension in high income countries ranged from 4.7 to 54.4% while that of LMICs ranged from 8.7 to 45.9%. It was highest in USA (21.2-54.4%) and lowest in Africa (8.7-45.9%). There was no statistically significant difference found in the prevalence of hypertension between ART exposed and ART naïve groups, however, this was partly attributed to the differences in duration of ART use and thus they report that the class of ART used may play a role in progression to hypertension in these patients.

Xu et al (42) reported that prevalence of hypertension in PLHIV ranged between 4.0% to 67.0%. The global prevalence of hypertension in PLHIV was found to be 25.2% and more so higher with increasing age (40.3% ≥ 50 years of age). However, they noted that the prevalence in PLHIV on ART was 34.7% while that of those who were ART naïve was 12.7%. This systematic review included 36 cross-sectional studies which are all part of Table 3.Naidu et al (34) also assessed the prevalence of hypertension as part of MS and reported a mean prevalence of 32.3% amongst all the cross-sectional studies. The mean prevalence's for South America, Asia and Africa has been reported as 35.2%, 24.8% and 21.6% respectively. This systematic review also highlights that the prevalence of hypertension in PLHIV on ART is higher than that of ART naïve, however, they did not provide any percentages for the said groups.

Discussion

Summary of main results

In our overview we identified 7 completed systematic reviews from 2009 to date. The last search conducted for primary studies within these systematic reviews was in December 2016.

These systematic reviews have included 142 cross-sectional studies conducted on participants from around the world with variable methodological quality as none of them addressed all the domains on the AMSTAR 2 tool. Of note, despite the fact that the systematic reviews included in this overview have been published very close to each other and their search strategies have included cross-sectional studies conducted over a long period of time, there is a very poor overlap of these cross-sectional studies between the systematic reviews which poses a threat to their quality as well as the evidence generated by them as ideally the most recent systematic review would include all previous primary studies unless a similar systematic review was done a decade ago which included the older primary studies hence the recent one would consolidate the more recent ones. Only one systematic review (34) assessed the prevalence of MS and reported a high mean prevalence of 30.5% of MS in Africa followed by Asia and South America.

The prevalence of depression, MDD and depressive symptoms ranged from as low as 3% to 64% in PLHIV on ART with high prevalence's occurring in LMICs; primarily the African population. The prevalence of type II diabetes mellitus ranged from 7% to 48.6% where the mean prevalence was reported to be lowest (18.1%) in Africa and higher prevalence's were noted in people on ART compared to ART naïve patients. The prevalence of dyslipidemia ranged from 6.3% to 100%, the lowest mean prevalence was yet again in Africa (32.8%). On individual assessments of the lipid profile, both low HDL cholesterol and hypertriglyceridemia were found to have lower prevalence's in the African population compared to others and the use of ART was found to be associated with higher prevalence's. The prevalence of hypertension ranged from 4.0% to 67% globally with higher prevalence's of 35.2% in South America and 24.8% in Asia, while the African population exhibited a lower prevalence of 21.6%. Patients over 50 years of age have higher prevalence's compared

to younger people and the use of ART is associated with an increased prevalence of hypertension in PLHIV.

How these findings link with existing research/overall completeness and applicability of evidence

Multi-morbidity reported as MS in Naidu et al was reported to have high prevalence in the ART group when comparisons were made between those receiving and not receiving ART. This is in keeping with the results of Nguyen et al (20).

Depression in this overview of systematic reviews ranged from 3% to 64% with highest prevalence in the African continent. A cross-sectional study conducted in Ethiopia in 2018 (44) showed a high prevalence of depression (48.6%) in HIV patients who were receiving ART's. Similarly, Rong et al (45) also reports a high prevalence of depression (40.3%) in the Chinese population with HIV on ART treatment. These findings point to the fact that depression prevails in PLHIV despite being on ART. This may hinder their quality of lives if unrecognized or untreated and lead to poor ART adherence.

The risk of developing type II diabetes mellitus is two to five times more in PLHIV who are receiving ART (22) hence increasing its prevalence. Lowest prevalence's have been reported in African compared to other countries. Thus is the case in Cameroon and Malawi where the prevalence's have been reported to be as low as 2% and 4.1% respectively (46)(47).

Dyslipidemia is highly prevalent in PLHIV. Dave et al have similarly shown a high prevalence of dyslipidemia in both ART consuming (85%) and ART naïve patients (90%) (48). However, the prevalence of hypertriglyceridemia is seen to be higher among those on ART whilst a higher prevalence of low HDL levels is noted in ART naïve patients in this overview which was also demonstrated by Dave et al but these findings are questionable as some studies show the opposite results (49).

Hypertension is also highly prevalent in PLHIV which is in keeping with Dimala et al (50) (38% had hypertension on ART and 19% in the ART naïve groups) and Nduka et al (51) (14.5% vs 10.5% in ART and ART naïve groups respectively). Follow-up study showed that the baseline prevalence in HIV patients was 19.3% and 12 months after initiation of ART the prevalence increased to 50.2% (50) which demonstrates an increased risk of developing hypertension in ART consumers.

A high burden of multimorbidity which approximates to about 50% was noted in this overview which calls for increased surveillance and strengthened models for integrated approach to treating and screening PLHIV. Of the many approaches suggested, one is strengthening the health workforce through task shifting and capacity building by educating the health cadres so that they are competent and patient-focused (14)(18). Pragna et al in their systematic review assessed NCDs in low- and middle- income countries where they identified barriers to NCD care which include poor infrastructure, interrupted supply of NCD medications, inadequate diagnostics, lack of NCD specialists and general health care workers etc.(52). This poses a threat to sustaining HIV-NCD integrated care and needs to be focused on in order to assess the outcomes of integration and be able to cost effectively provide service to PLHIV(17).

Strengths and Limitations

We have a strong search methodology as we conducted a comprehensive search in 7 databases, 2 reviewers performed screening independently and data extraction was done by one author which was checked by the second author. Our results are not restricted to any continent or population and we have assimilated all the prevalence's to provide a range of values for the global prevalence's of NCD's as reported in the cross-sectional studies

included in the systematic reviews. We conducted our search in February 2018 and of the included systematic reviews the latest one conducted their search in December 2016. Hence, this overview does not include any cross-sectional studies published thereafter i.e. in 2017/2018. Also, cross-sectional studies which were not included in any of our included systematic reviews are not part of this overview.

This is the first overview conducted on the said topic and it includes 7 systematic reviews. It can be used to serve as a base from which further improved systematic reviews can be conducted as we observed gaps in the conduct of systematic reviews which needs to be addressed to authors who are going to embark on conducting systematic reviews in the future. It can also be used to inform policies and practices. We did not extract prevalence data from the individual cross-sectional studies and adherence to ART treatment is unknown. We only used some of the AMSTAR 2 tool domains to assess methodological quality. This overview does not contain any information on the types and duration of ART use by the patients as data were not available across all the systematic reviews and importantly it highlights that multimorbidity has been scarcely researched on as we only have one systematic review assessing its prevalence in PLHIV

Conclusions

Implications for practice

The high burden of NCD's in PLHIV calls for dedicated efforts to identify those with NCD's early through screening programs and to implement comprehensive treatment for those diagnosed.

Implications for research

Primary/cross-sectional studies need to be conducted which focus on assessing prevalence of multimorbidity with NCD's instead of focusing on one NCD. Complete information should be provided by investigators on adherence, duration and type of ART received by participants. Furthermore, authors conducting systematic reviews need to follow the PRISMA reporting guidelines.

Abbreviations

AIDS – Acquired immunodeficiency syndrome

ART – Antiretroviral Therapy

DSM 5 - Diagnostic and Statistical Manual of Mental Disorders Fifth Edition

FBG – Fasting Blood GlucoseHbA1c - Glycated Hemoglobin

HDL - High Density Lipoproteins

HIC – High Income Countries

HIV – Human immunodeficiency virus

LDL – Low Density Lipoproteins

LMIC – Low to Middle Income Countries

MS – Metabolic Syndrome

NCD's – Non-communicable diseases

OGTT - Oral Glucose Tolerance Test

PLHIV – People living with HIV

RBG - Random Blood Glucose

SSA – Sub Saharan Africa

UNAIDS - United Nations Program on HIV and AIDS

Declarations

Acknowledgements

We would like to thank Miss. Anel Schoonees for conducting the searches on the databases.

Funding

Funding for this Overview was provided by the Collaboration for Evidence-based Healthcare and Public Health in Africa (CEBHA+), as part of the Research Networks for Health Innovation in Sub-Saharan Africa Funding Initiative of the German Federal Ministry of Education and Research.

Availability of data

We have provided all the necessary documents which are not part of the manuscript as additional files and appendices.

Author's contributions

Both the authors were involved in writing the protocol, screening and data extraction, and drafting and finalizing the manuscript.

Ethics approval

Not applicable.

Consent for publications

Not applicable.

Competing interests

The Authors declare no competing interests of whatsoever.

Table 3: Mapping of Cross-sectional studies included in the completed systematic reviews

No.	Study ID	Sample size	Country	ART status (%)	Dyslip-idemia	Hyper-tension	Diabe-tes	Depres-sion	Naidu 2017	Prioreschi 2017	Brandt 2009	XU 2017	Nguyen 2015	Lowther 2014	Bernard 2017
1	Adewuya 2008	87	Nigeria	100				√						X	X
2	Adewuya 2009	190	Nigeria	100				√						X	
3	Alciati 2001	90	Italy	95.5				√						X	
4	Alemu 2012	1722	Ethiopia	100				√							X
5	Alencastro 2012	1240	Brazil	65.7	√	√	√		X						
6	Ammassari 2004	135	Italy	100				√						X	
7	Antonello 2015	1009	Brazil	73		√						X			
8	Asangbeh 2015	200	Cameroon	100				√							X
9	Awotedu 2010	86	South Africa	100	√	√	√		X						
10	Bajaj 2013	70	India	67	√	√	√		X						
11	Balderson 2013	452	United States	100		√							X		
12	Bayon 2012	799	Spain	100				√						X	
13	Begovac 2015	254	Serbia	100		√						X			
14	Belenky 2014	403	Tanzania	100				√							X
15	Berhane 2012	313	Ethiopia	100	√	√	√		X				X		
16	Berhe 2013	269	Ethiopia	100				√							X
17	Bernardino 2011	310	Spain	71		√							X		
18	Besa 2015	185	Zambia	98.4				√							X
19	Bhat 2013	299	India	100				√						X	
20	Bhengu 2011	149	South Africa	100				√						X	
21	Bongongo 2013	117	South Africa	100				√						X	X
22	Bonjoch 2014	970	Spain	100		√						X			

23	Braganca 2011	130	Portugal	100				√						X	
24	Broom 2012	180	Australia	88		√							X		
25	Bryant 2015	79	United States	100		√						X			
26	Buathong 2009	379	Thailand	100				√						X	
27	Buchacz 2013	3166	United States	100		√						X			
28	Cahn 2010	3966	Multisite *	100	√	√	√		X						
29	Calza 2014	894	Italy	77.5		√						X			
30	Cha 2008	215	United States	100				√						X	
31	Chan 2013	733	Australia	83		√							X		
32	Chu 2011	854	United States	76		√							X		
33	Cianflone 2011	223	United States	83		√						X			
34	Clarke 2010	50	Jamaica	79				√						X	
35	De 2012	94	India	100				√						X	
36	De Socio 2014	1182	Italy	94		√							X		
37	De souza 2011	1245	Brazil	100				√						X	
38	Diaz 2016	2960	Brazil	100		√						X			
39	Dimala 2016	100	Cameroon	100		√						X			
40	Dimodi et al 2014	463	Cameroon	75.2	√	√	√		X						
41	Diouf 2012	242	Senegal	100		√						X	X		
42	Divala 2016	952	Malawi	95.9		√						X			
43	Do 2010	300	Botswana	81.3				√						X	X
44	Do 2013	615	Vietnam	100				√						X	
45	Fabbiani 2013	245	Italy	93.9		√						X	X		
46	Farley 2010	399	Nigeria	40				√							X
47	Farrant 2012	385	South Africa	98.4				√						X	
48	Freeman 2007/8	900	South Africa	18				√			X				

49	Galli 2012	2345	Italy	91.5		√						X			
50	Garvie 2011	12	United States	45				√						X	
51	Gaynes 2012	400	Cameroon	100				√						X	X
52	Gibbie 2006	78	Australia	94				√						X	
53	Gonzalez 2011	91	United States	100				√						X	
54	Gordillo 1999	366	Spain	100				√						X	
55	Hejazi 2012	340	Malaysia	100		√							X		
56	Idiculla 2011	60	India	50	√	√	√		X						
57	Ikeda 2013	1240	Brazil	65.7		√						X			
58	Isasti 2013	196	Spain	94.4		√						X			
59	Iwuala 2015	145	Nigeria	100		√						X			
60	Janiszewski 2011	2322	Italy	100		√							X		
61	Jantarapakde 2014	580	Thailand	71	√	√	√		X						
62	Judd 2005	129	Australia	93				√						X	
63	Julius 2009	304	South Africa	100	√	√	√		X				X		
64	Kagaruki 2014	671	Tanzania	52.8		√	√			X			X		
65	Kagee 2010	85	South Africa	60				√							X
66	Kagee 2013	200	South Africa	100				√							X
67	Karambe 2010	286	Mali	50				√							X
68	Keltner 2012	397	United States	75				√						X	
69	Kitshoff 2012	146	South Africa	100				√							X
70	Knowlton 2011	154	United States	83				√						X	
71	Kong 2012	7034	United States	100				√						X	
72	L'akoa 2013	100	Cameroon	67				√							X
73	Lawler 2011	120	Botswana	97.5				√						X	X
74	Maganga 2015	301	Tanzania	50.2			√			X					

75	Maj 1994	408	Zaire, Kenya	47.3				√			X				
76	Malangu 2014	190	Botswana	100	√	√	√		X						
77	Manuthu 2008	295	Kenya	45		√	√			X			X		
78	Martin 2014	263	Uganda	100				√							X
79	Martinez 2008	421	Uganda	57				√							X
80	Mbunkah 2014	173	Cameroon	50	v	√	√		X						
81	Medina-Torne 2012	707	United States	72		√						X	X		
82	Menezes 2011	213	Brazil	100		√						X			
83	Michel 2010	328	France	91				√						X	
84	Mital 2013	200	India	50	√	√	√		X						
85	Mohammed 2015	393	Ethiopia	72.3		√	√			X		X			
86	Monteiro 2012	261	Brazil	89		√						X			
87	Muronya 2011	174	Malawi	100		√						X	X		
88	Myer 2008	465	South Africa	48				√			X				X
89	Myerson 2014	4278	United States	87.5		√						X	X		
90	Nakimuli-Mpungu 2011	500	Uganda	100				√						X	X
91	Nakimuli-Mpungu 2013	400	Uganda	100				√						X	X
92	Nakku 2013	618	Uganda	64.6				√							X
93	Negash 2013	355	Ethiopia	100				√							X
94	Nel 2013	96	South Africa	100				√						X	X
95	Nery 2013	294	Brazil	66.3		√						X			
96	Ngo 2013	40	Uganda	100				√							X
97	Nozaki 2011	518	Zambia	100				√						X	
98	Nsagha 2015	215	Cameroon	74.4	√	√				X		X			
99	Nyamathi 2013	68	India	100				√						X	

100	Ogunmola 2014	250	Nigeria	32.2		√						X			
101	Olalla 2013	388	Spain	86.1		√						X			
102	Olisah 2010	310	Nigeria	100				√						X	X
103	Overton 2012	670	United States	79		√						X			
104	Owolabi 2012	300	Nigeria	92				√						X	
105	Pacheco 2015	591	Brazil	89		√						X			
106	Palmer 2011	451	Canada	100				√						X	
107	Pappin 2012	716	South Africa	100				√						X	X
108	Parikh 2015	150	United States	100		√						X			
109	Patel 2013	454	United States	82		√						X			
110	Peck 2014	301	Tanzania	50.2		√						X			
111	Peretti-Watel 2006	2932	France	53				√						X	
112	Peterson 2012	252	Gambia	100				√						X	
113	Poupard 2007	200	Senegal	100				√			X			X	X
114	Pumpradit 2010	64	Thailand	100				√						X	
115	Rabkin 2000	133	United States	84-91[#]				√						X	
116	Reinsch 2012	803	Germany	85.4		√						X	X		
117	Roux 2009	1809	France	100				√						X	
118	Sarna 2008	310	India	100				√						X	
119	Schoesson 2007	193	Sweden	100				√						X	
120	Seth 2014	3538	Kenya, Namibia, Tanzania	64				√							X
121	Sherer 2014	2035	Global	100		√							X		
122	Signorini 2012	819	Brazil	76	√	√	√		X						
123	Silva 2009	215	Brazil	100	√	√	√		X						

124	Silveria 2012	246	Brazil	100				√						X	
125	Simbayi 2007	1063	South Africa	50				√			X				X
126	Simoni 2007	136	United States	89.7				√						X	
127	Starace 2002	268	Italy	66.7				√						X	
128	Sulyok 2015	136	Hungary	92		√						X			
129	Sumari-de Boer 2012	201	Netherlands	100				√						X	
130	Tesfaye 2014	374	Ethiopia	50.3	√	√	√		X	X					
131	Tongma 2013	111	United States	100		√						X			
132	Villamar 2011	114	Ecuador	88.5	√	√	√		X						
133	Viskovic 2013	110	Croatia	100		√						X			
134	Werberich 2013	184	Brazil	100	√	√	√		X						
135	Wolfe 2006	112	Botswana	100				√						X	
136	Wolitski 2009	637	United States	97				√						X	
137	Wouters 2012	716	South Africa	100				√						X	X
138	Wroe 2015	292	Rwanda	100				√							X
139	Wu 2014	920	Taiwan	>95		√						X	X		
140	Yeji 2014	272	South Africa	100				√							X
141	Yen 2004	41	China	100				√						X	
142	Zhang 2012	563	Canada	100				√						X	

*Argentina, Brazil, Colombia, Ecuador, Peru, Venezuela

#ART 84% of the 75 men and 91% of the 58 women

Table 4: Table of Excluded systematic reviews

Study ID	**Reason for exclusion**
Alessandra 2016 (53), Alexandra 2016 (54), Amir 2017 (55), Dillon 2013 (53), Dimala 2017 (54), Echecopar-Sabogal 2017 (55), Nduka 2016 (41), Nduka 2017 (56), Piliero 2003 (57)	Assessed association between NCDs and HIV and not prevalence of NCD in HIV patients
Angkurawaranon 2016 (56)	Had separate groups of HIV/ART/Hypertension that were matched
Balt 2013 (57), Brown 2008 (58), Lo 2011 (59), McKeage 2009 (60), Watkins 2011 (61), Watkins 2016 (62), Willig 2016 (63)	Not a cross-sectional study design
Dube 2000 (64), Polo 2006 (65)	Clinical guideline
Nguyen 2016 (20)	Assessed the prevalence of metabolic syndrome but did not report on its individual components
Bongani 2017 (66), Casaretti 2011 (67), Chidozie 2014 (68), D'Ascenzo 2012 (69), Ena 2003 (70), Green 2002 (71), Langebeek 2014 (72), Maurice 2017 (73), Mayston 2012 (74), Melroe 1999 (75), Memiah 2014 (75), Nduka 2015 (76), Pantelic 2015 (77), Reust 2011 (78), Rueda 2016 (79), Samson 2017 (80), Swenson 2006 (81), Tao 2017 (82), Tsai 2014 (83), Unachukwu 2009 (84), Uthman 2014 (85), Yuen 2016 (86)	Did not the assess outcomes that we are interested in

Additional files

Additional file 1: Search strategy

Search Output from MEDLINE (via PubMed)

No date limitations

Search date: 27 Feb 2018

Results: 158

No.	Query	Items found
#15	#12 OR #14	158
#14	Search #3 AND #10 Sort by: Best Match Filters: Systematic Reviews; Meta-Analysis	346
#13	Search #3 AND #10	4529
#12	Search #3 AND #10 AND #11	35
#11	Search ((((("systematic review") OR (("meta-analysis" OR "meta analysis")))[title/abstract] OR sysrev_methods [sb]) OR "Meta-Analysis"[Publication Type])	100043
#10	Search #4 OR #5 OR #6 OR #7 OR #8 OR #9	1361077
#9	Search (((((depression OR depressive)))[title/abstract] OR "Depression"[Mesh]) OR "Depressive Disorder"[Mesh])	187994
#8	Search ((((dyslipidaemia OR dyslipidemia OR cholesterol OR LDL OR HDL OR triglyceride OR triglycerides OR low density lipoprotein OR high density lipoprotein OR low-density lipoprotein OR high-density lipoprotein)))[title/abstract] OR "Dyslipidemias"[Mesh])	73403
#7	Search ("Hypertension"[Mesh] OR (hypertension OR "blood pressure"))	726226
#6	Search ((((diabetes OR "diabetes mellitus")))[title/abstract] OR "Diabetes Mellitus"[Mesh])	377084
#5	Search ("noncommunicable disease" OR "noncommunicable diseases" OR "non-communicable disease" OR "non-communicable diseases" OR NCD OR NCDs OR "Noncommunicable Diseases"[Mesh])	10613
#4	Search (((((comorbidity OR co-morbidity OR "co morbidity" OR multimorbidity OR multi-morbidity OR "multi morbidity")))[title/abstract] OR "Multimorbidity"[Mesh]) OR "Comorbidity"[Mesh])	91585
#3	#1 AND #2	113375
#2	Search ((((antiretroviral agents [Mesh] OR antiretroviral therapy, highly active [Mesh]))) OR ((Antiretroviral* OR ((anti) AND (retroviral*)) OR ARV* OR ART OR "antiretroviral therapy" OR HAART OR ((highly) AND (active) AND (antiretroviral*) AND (therap*)) OR ((anti) AND (hiv)) OR ((anti) AND (acquired immunodeficiency)) OR ((anti) AND (acquired immuno-deficiency)) OR ((anti) AND (acquired immune-deficiency)) OR ((anti) AND (acquired immun*) AND (deficienc*)))))	235672
#1	Search (((((HIV OR hiv-1 OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immune deficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR ((human immun*) AND (deficiency virus)) OR acquired immunodeficiency syndromes OR acquired immune deficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR ((acquired immun*) AND (deficiency syndrome)) OR HIV/AIDS)))) OR ((HIV infections [MeSH] OR HIV [MeSH])))	389357

Search Output from Cochrane Database of Systematic Reviews (CDSR)

No date limitations

Search date: 27 Feb 2018

Results: 966

1	HIV or hiv-1 or hiv-2* or hiv1 or hiv2 or hiv infect* or human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus	19064
2	((human immun*) and (deficiency virus)) or acquired immunodeficiency syndromes or acquired immune deficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome	2008
3	((acquired immun*) and (deficiency syndrome))	1350
4	HIVAIDS	4
5	MeSH descriptor: [HIV Infections] explode all trees	9825
6	MeSH descriptor: [HIV] explode all trees	3036
7	#1 or #2 or #3 or #4 or #5 or #6	19497
8	MeSH descriptor: [Anti-Retroviral Agents] explode all trees	4195
9	MeSH descriptor: [Antiretroviral Therapy, Highly Active] explode all trees	1289
10	antiretroviral*	6098
11	anti and retroviral*	847
12	ARV* or ART or "antiretroviral therapy" or HAART	96034
13	highly and active and antiretroviral* and therap*	2121
14	anti and hiv	5237
15	anti and "acquired immunodeficiency"	477
16	anti and "acquired immuno-deficiency"	58
17	anti and "acquired immune-deficiency"	682
18	anti and "acquired immun*" and deficienc*	713
19	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18	99271
20	#7 and #19	10776
21	MeSH descriptor: [Comorbidity] explode all trees	3564
22	MeSH descriptor: [Multimorbidity] explode all trees	4
23	comorbidity or co-morbidity or "co morbidity" or multimorbidity or multi-morbidity or "multi morbidity"	11571
24	#21 or #22 or #23	11571
25	MeSH descriptor: [Noncommunicable Diseases] explode all trees	0
26	"noncommunicable disease" or "noncommunicable diseases" or "non-communicable disease" or "non-communicable diseases" or NCD or NCDs	402
27	#25 or #26	402
28	MeSH descriptor: [Diabetes Mellitus] explode all trees	21495
29	diabetes or "diabetes mellitus"	52709
30	#28 or #29	54092
31	hypertension or "blood pressure"	89630
32	MeSH descriptor: [Hypertension] explode all trees	15899
33	#31 or #32	89630
34	dyslipidaemia or dyslipidemia or cholesterol or LDL or HDL or triglyceride or triglycerides or "low density lipoprotein" or "high density lipoprotein" or "low-density lipoprotein" or "high-density lipoprotein"	34845
35	MeSH descriptor: [Dyslipidemias] explode all trees	5785
36	#34 or #35	35557
37	depression or depressive	55189
38	MeSH descriptor: [Depressive Disorder] explode all trees	9229
39	MeSH descriptor: [Depression] explode all trees	7658
40	#37 or #38 or #39	55229
41	#24 or #27 or #30 or #33 or #36 or #40	204541
42	#20 AND #41	2117
43	#42 in Cochrane Reviews (Reviews and Protocols)	966

Search Output from Database of Abstracts of Reviews of Effects (DARE)

No date limitations; but DARE has only been updated until 2015: Issue 2 of 4, April 2015

Search date: 27 Feb 2018

Results: 121

1	HIV or hiv-1 or hiv-2* or hiv1 or hiv2 or hiv infect* or human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus	19064
2	((human immun*) and (deficiency virus)) or acquired immunodeficiency syndromes or acquired immune deficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome	2008
3	((acquired immun*) and (deficiency syndrome))	1350
4	HIVAIDS	4
5	MeSH descriptor: [HIV Infections] explode all trees	9825
6	MeSH descriptor: [HIV] explode all trees	3036
7	#1 or #2 or #3 or #4 or #5 or #6	19497
8	MeSH descriptor: [Anti-Retroviral Agents] explode all trees	4195
9	MeSH descriptor: [Antiretroviral Therapy, Highly Active] explode all trees	1289
10	antiretroviral*	6098
11	anti and retroviral*	847
12	ARV* or ART or "antiretroviral therapy" or HAART	96034
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15	anti and "acquired immunodeficiency"	477
16	anti and "acquired immuno-deficiency"	58
17	anti and "acquired immune-deficiency"	682
18	anti and "acquired immun*" and deficienc*	713
19	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18	99271
20	#7 and #19	10776
21	MeSH descriptor: [Comorbidity] explode all trees	3564
22	MeSH descriptor: [Multimorbidity] explode all trees	4
23	comorbidity or co-morbidity or "co morbidity" or multimorbidity or multi-morbidity or "multi morbidity"	11571
24	#21 or #22 or #23	11571
25	MeSH descriptor: [Noncommunicable Diseases] explode all trees	0
26	"noncommunicable disease" or "noncommunicable diseases" or "non-communicable disease" or "non-communicable diseases" or NCD or NCDs	402
27	#25 or #26	402
28	MeSH descriptor: [Diabetes Mellitus] explode all trees	21495
29	diabetes or "diabetes mellitus"	52709
30	#28 or #29	54092
31	hypertension or "blood pressure"	89630
32	MeSH descriptor: [Hypertension] explode all trees	15899
33	#31 or #32	89630
34	dyslipidaemia or dyslipidemia or cholesterol or LDL or HDL or triglyceride or triglycerides or "low density lipoprotein" or "high density lipoprotein" or "low-density lipoprotein" or "high-density lipoprotein"	34845
35	MeSH descriptor: [Dyslipidemias] explode all trees	5785
36	#34 or #35	35557
37	depression or depressive	55189
38	MeSH descriptor: [Depressive Disorder] explode all trees	9229
39	MeSH descriptor: [Depression] explode all trees	7658
40	#37 or #38 or #39	55229
41	#24 or #27 or #30 or #33 or #36 or #40	204541

42	#20 AND #41	2117
43	#42 in Other Reviews	121

Search Output from CINAHL (EBSCOHost)

Search date: 27 Feb 2018

No date limits

Results: 49

Search Terms	Search Options	
S46	S21 AND S41 AND S45	View Results (49)
S45	S42 OR S43 OR S44	View Results (70,001)
S44	MH systematic review	View Results (36,541)
S43	AB "systematic review" OR meta-analysis	View Results (28,494)
S42	PT "systematic review" OR meta-analysis	View Results (50,859)
S41	S24 OR S25 OR S28 OR S31 OR S35 OR S38	View Results (247,959)
S38	S36 OR S37	View Results (77,053)
S37	MH depression	View Results (54,589)
S36	AB depression or "depressive disorder"	View Results (48,547)
S35	S32 OR S33 OR S34	View Results (24,701)
S34	MH hyperlipidemia	View Results (6,
S33	AB hyperlipidemia	View Results (1,705
S32	AB dyslipidaemia or dyslipidemia or cholesterol or LDL or HDL or triglyceride or triglycerides or "low density lipoprotein" or "high density lipoprotein" or "low-density lipoprotein" or "high-density lipoprotein"	View Results (19,813)
S31	S29 OR S30	View Results (63,161)
S30	MH hypertension	View Results (29,138)
S29	AB hypertension OR "blood pressure"	View Results (47,216)
S28	S26 OR S27	View Results (80,493)
S27	MH diabetes mellitus	View Results (35,297)
S26	AB diabetes OR "diabetes mellitus"	View Results (58,542)
S25	TX "noncommunicable disease" or "noncommunicable diseases" or "non-communicable disease" or "non-communicable diseases" or NCD or NCDs	View Results (1,923)
S24	S22 OR S23	View Results (44,832)
S23	MH comorbidity	View Results (29,459)
S22	TX comorbidity or co-morbidity or "co morbidity" or multimorbidity or multi-morbidity or "multi morbidity"	View Results (44,832)

S21	S7 AND S20	**View Results** (15,713)
S20	S17 OR S18 OR S19	**View Results** (47,940)
S19	MH Anti-Retroviral Agents	**View Results** (1,857)
S18	MH Antiretroviral Therapy, Highly Active	**View Results** (2,991)
S17	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16	**View Results** (47,940)
S16	TX anti and "acquired immun*" and deficienc*	**View Results** (115)
S15	TX anti and "acquired immune-deficiency"	**View Results** (74)
S14	TX anti and "acquired immuno-deficiency"	**View Results** (2)
S13	TX anti and "acquired immunodeficiency"	**View Results** (919)
S12	TX anti and hiv	**View Results** (11,134)
S11	TX highly and active and antiretroviral* and therap*	**View Results** (3,883)
S10	TX ARV* or ART or "antiretroviral therapy" or HAART	**View Results** (40,232)
S9	TX anti and retroviral*	**View Results** (2,193)
S8	TX antiretroviral*	**View Results** (9,282)
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6	**View Results** (77,216)
S6	MH Human Immunodeficiency Virus	**View Results** (2,839)
S5	MH HIV infections	**View Results** (38,900) **View Details** **Edit**
S4	TX HIVAIDS	**View Results** (16)
S3	TX ((acquired immun*) and (deficiency syndrome))	**View Results** (711)
S2	TX ((human immun*) and (deficiency virus)) or acquired immunodeficiency syndromes or acquired immune deficiency syndrome or acquired immuno-deficiency syndrome or acquired immune-deficiency syndrome	**View Results** (13,885)
S1	TX HIV or hiv-1 or hiv-2* or hiv1 or hiv2 or hiv infect* or human immunodeficiency virus or human immune deficiency virus or human immuno-deficiency virus or human immune-deficiency virus	**View Results** (71,286)

Search Output from Web of Science – Core Collection

Search date: 27 Feb 2018

No date limits (1970 to present)

Results: 152

# 17	**152**	#16 AND #15 *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit

# 16	237,822	**TOPIC:** ((systematic review) OR meta-analysis) *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 15	5,667	#14 AND #5 *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 14	1,649,568	#13 OR #12 OR #9 OR #8 OR #7 OR #6 *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 13	417,078	**TOPIC:** (depression OR (depressive disorder)) *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 12	352,118	#11 OR #10 *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 11	111,774	**TOPIC:** ((low-density lipoprotein) or (high-density lipoprotein)) *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 10	324,619	**TOPIC:** (cholesterol OR dyslipidemia OR LDL or HDL or triglyceride) *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 9	532,145	**TOPIC:** (hypertension OR "blood pressure") *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 8	477,881	**TOPIC:** (diabetes OR "diabetes mellitus") *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 7	6,246	**TOPIC:** (non-communicable disease OR NCD) *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 6	68,866	**TOPIC:** (comorbidity OR multimorbidity) *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 5	71,454	#4 AND #3 *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 4	738,368	#2 OR #1 *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit

# 3	357,793	**TOPIC:** (antiretroviral OR ART OR HAART OR "highly active antiretroviral*" OR ARV) *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 2	481,320	**TOPIC:** (AIDS OR HIV/AIDS OR "acquired immunodeficiency") *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	Edit
# 1	351,763	**TOPIC:** (HIV* OR "HIV infect*" OR "human immunodeficiency virus") *Indexes=SCI-EXPANDED, SSCI, CPCI-S, IC Timespan=All years*	

Search Output from PROSPERO

Search date: 27 Feb 2018

No date limits

Results: 49

(HIV OR AIDS OR HIV/AIDS OR Human Immunodeficiency Virus OR acquired immunodeficiency syndrome) AND (anti-HIV drugs OR antiretroviral OR anti-retroviral OR ART OR ARV OR HAART OR highly-active antiretroviral) AND (comorbidity OR co-morbidity OR multimorbidity OR non-communicable disease OR noncommunicable disease OR diabetes OR hypertension OR blood pressure OR cholesterol OR dyslipidemia OR dyslipidaemia OR hyperlipidaemia OR hyperlipidemia OR LDL OR HDL OR triglycerides OR lipoprotein OR depresssion OR depressive disorder)

Search Output from Epistemonikos

No date limit

Search date: 27 Feb 2018

Search results = 105

HIV AND antiretroviral AND (comorbidities OR diabetes OR hypertension OR blood pressure OR cholesterol OR dyslipidemia OR hyperlipidemia OR depression OR depressive) [Filters: protocol=no, classification=systematic-review]

Additional File 2: AMSTAR 2 assessment of included reviews

AMSTAR 2 Criteria	Bernard 2017	Brandt 2009	Lowther 2014	Naidu 2017	Nguyen 2015	Prioreschi 2017	Xu 2017
Did the research questions and inclusion criteria for the review include the components of PICO? Was the research question clear? **<u>NOTE:</u> Timeframe, Intervention & comparator are not applicable to cross-sectional studies.**	Population is HIV+ adults in SSA and outcomes are prevalence and factors associated with depression.	Population is HIV+ adults and the outcome is mental health.	Population is HIV+ adults and outcomes are the prevalence of depression, anxiety or the experience of stigma in HIV infected persons on antiretroviral therapy.	Population is HIV+ adults in developing countries and the outcomes are prevalence of Metabolic syndrome & its components.	Population is HIV+ and Outcomes are Burden, Determinants and Pharmacological Management of Hypertension.	Population is PLHIV and Outcome is development of type II diabetes mellitus.	Population is over 16yr PLHIV, Outcome is prevalence of Hypertension globally
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	There is no statement about protocol being written a priori or any deviations made from the protocol. Also, the PRISMA checklist shows NO protocol registration number.	There is no statement about protocol being written a priori and any revisions/deviations from protocol.	There is no statement about protocol being written a priori and any revisions/deviations from protocol. No supplementary documents are attached.	There is no statement about protocol being written a priori and any revisions/deviations from protocol, methods say review done in accordance with PRISMA guidelines but no supplementary document to support this.	Protocol developed with research question, search strategy, inclusion/exclusion criteria and ROB assessment but it was not registered.	Protocol available on PROSPERO via the registration number provided in the review, they had planned for meta analysis and assessing heterogeneity.	Not mentioned that a protocol was developed/ registered.
Did the review authors use a comprehensive literature	More than 2 databases were searched,	More than 2 databases searched, reference	More than 2 databases searched, keywords	More than 2 databases searched, and keywords	Only searched in 1 database	Searched in 4 databases, key words provided, and	Searched in 2 databases, keywords provided,

search strategy?	keywords are provided, and restriction was on age (which is justified by inclusion criteria).	lists were searched, and keywords are listed. They included only published studies and English studies. Age restrictions were also applied.	provided, only articles in English and French language accepted. Reference lists were also searched. Grey literature and expert opinion are not mentioned.	have been listed.		restrictions justified.	restricted to English articles
Did the review authors perform study selection in duplicate?	Not mentioned who, and how many people did the study selection.	Not mentioned who and how many people did study selection.	Only 1 author did the selection against the inclusion and exclusion criteria. When unclear, he consulted the other author.	More than 2 reviewers performed study selection.	Not mentioned who and how many people did study selection.	2 reviewers screened the titles and abstracts and consensus was reached by discussion.	Not mentioned; Under author contributions **only one author seems to have done study selection.**
Did the review authors perform data extraction in duplicate?	Not mentioned who, and how many people performed data extraction.	Not mentioned who and how many people performed data extraction.	Not clear. Not mentioned who and how many people performed data extraction. They have stated only stated that they had a form onto which data was extracted.	Not mentioned clearly whether the same people who assessed eligibility also extracted data. All the information is summarized under data extraction in one paragraph.	Not mentioned who and how many people performed data extraction.	2 reviewers were involved in DE and based on AMSTAR "at least two reviewers achieved consensus on which data to extract from included studies. Prioreschi - One reviewer (AP) reassessed data extraction for all eligible full texts. Standardized forms were used to extract data.	Two authors extracted data and upon differences consensus was by discussion

Did the review authors provide a list of excluded studies and justify the exclusions?	They have not listed excluded studies even in the supplementary documents.	They have not listed excluded studies.	They have not listed excluded studies.	They have not listed excluded studies.	They have not listed excluded studies.	They have not listed excluded studies.	They have not listed excluded studies.
Did the review authors describe the included studies in adequate detail? **<u>NOTE:</u> Timeframe, Intervention & comparator are not applicable to cross-sectional studies.**	Population (age, HIV and ART status), Outcome (prevalence of depression/depressive symptoms) and type of study well are well described.	Population and study parameters are well described but outcome is mentioned insufficiently	Not well described in the tables. Made an effort.	Population is detailed, Outcomes are described as prevalence's of MS and its components, And the study design is mentioned on the heading of tables.	Population, outcome and study setting are all described in adequate detail.	Population, outcome and study setting are all described in adequate detail	Table of included studies has all important details on PICO
Did the review authors report on the sources of funding for the studies included in the review?	Funding sources of individual studies aren't reported. There is no mention of any effort to look for it.	Funding sources of individual studies aren't reported. There is no mention of any effort to look for it.	Funding sources of individual studies aren't reported. There is no mention of any effort to look for it.	Funding sources of individual studies aren't reported nor efforts to look for it are mentioned	Funding sources of individual studies aren't reported nor efforts to look for it are mentioned	Funding sources of individual studies aren't reported nor efforts to look for it are mentioned	Funding sources of individual studies aren't reported nor efforts to look for it are mentioned
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Heterogeneity observed was very high with I^2 >80% between studies in most forest plots and the reasons are mentioned.	Narrative causes of heterogeneity were explored, no statistical tests done. They discussed the impact of this on the results of their review.	Sources and impact of the heterogeneity are discussed but not in detail.	They mention reasons of heterogeneity being different criteria's for diagnosing MS and components. Also, different groups (ART and ART naïve) have	They explained possible reasons for the wide range of prevalence's' observed	Not mentioned its impact; they did expect heterogeneity and I^2 is high, but reasons not explored	They explored heterogeneity and discussed its impact

				been included from the primary studies which are a cause of heterogeneity .			
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Meta-analysis done but no mention of publication bias/ no graphical or statistical illustration.	Meta-analysis not done. No mention of publication bias/ no graphical or statistical illustration.	Meta-analysis not done. Only mentioned about a small number of studies reporting a particular outcome, but no graphical or statistical illustration of publication bias.	Meta-analysis not done. No mention of publication bias/ no graphical or statistical illustration.	Meta-analysis not done. No mention of publication bias/ no graphical or statistical illustration.	Meta analysis has been done and they have mentioned that few studies have been included causing a bias but no graphical or statistical tests for publication bias have been done and there is no discussion about the likelihood and magnitude of impact of publication bias	Meta analysis has been done but no graphical or statistical tests for publication bias have been done. LOOK FOR THE FOREST PLOTS FROM APPENDIX
Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Source of funding mentioned and also declared that there were no conflicts of interest.	Source of funding is mentioned.	Source of funding mentioned and also declared that there were no conflicts of interest.	Source of funding mentioned and also declared no competing interests	Sources of funding mentioned, and conflicts declared	Sources of funding mentioned, and conflicts declared	Conflicts declared

Additional File 3: PRISMA reporting checklist – 2009

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	6 -7
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	11
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	12
METHODS			

Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	11
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	11
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	13
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	44 - 50
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	14
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	14
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	12
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	15
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	15
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	15

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	16,17,43
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	18
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	21-23
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	23

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	28-29
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	31
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	31,32
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	34

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PART B: Appendices

List of Appendices

1. Instructions for authors

2. Protocol

Appendix 1

Instructions for authors

The instructions for authors submitting to the BMC – Systematic Reviews journal have been summarized below. The link to this journal is https://systematicreviewsjournal.biomedcentral.com/

Research articles include any original primary research relating to the design, conduct or reporting of systematic reviews, as well as traditional systematic review results papers. Systematic Reviews strongly encourages that all datasets on which the conclusions of the paper rely should be available to readers deposited on repositories or in main manuscript or as additional files.

There is no word count for the manuscript submitted. Vancouver referencing style should be used, font size/type not stated. There is no limitation on the number of tables/figures. If it is less than A4 the it should be within the text, if A4 size then at the end. Longer than A4 should be provided as supplementary documents.

Reporting standards - for completed systematic reviews, Systematic Reviews requires the submission of a populated PRISMA checklist and flow diagram. The flow diagram should be included in the main body of the text and the checklist should be provided as an additional

file, both the flow diagram and the checklist should be referenced in the text. Submissions received without these elements will be returned to the authors as incomplete.

The manuscript should include the following:

1. The Declarations section including all of the subheadings.

2. The Title page should:

- present a title that includes, if appropriate, the study design e.g. for non-clinical or non-research studies a description of what the article reports
- list the full names, institutional addresses and email addresses for all authors
- indicate the corresponding author

3. The Abstract should not exceed 350 words. No references should be cited in the abstract and abbreviations should be minimized. Reports of systematic reviews should follow the PRISMA extension for abstracts. The abstract must include the following sections:

- Background: the context and purpose of the study
- Methods: how the study was performed, and statistical tests used
- Results: the main findings
- Conclusions: brief summary and potential implications
- Systematic review registration: if your systematic review is registered in a publicly accessible registry, include the name of the registry and registration number.

4. Three to ten keywords representing the main content of the article.

5. The Background section should explain the background to the study, its aims, a summary of the existing literature and why this study was necessary or its contribution to the field.

6. The Methods section should include:

- the aim, design and setting of the study
- the characteristics of participants or description of materials
- a clear description of all processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses
- the type of statistical analysis used, including a power calculation if appropriate.

7. The Results section - Should include the findings of the study including, if appropriate, results of statistical analysis which must be included either in the text or as tables and figures.

8. Discussion - This section should discuss the implications of the findings in context of existing research and highlight limitations of the study.

9. Conclusions - This should state clearly the main conclusions and provide an explanation of the importance and relevance of the study reported.

10. List of Abbreviations - If abbreviations are used in the text, they should be defined in the text at first use, and a list of abbreviations should be provided.

11. Declarations - All manuscripts must contain the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and material

- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

NOTE: If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Elaboration of some of the elements from the declaration section:

a) Availability of data and materials

All manuscripts must include an ‘Availability of data and materials’ statement. Data availability statements should include information on where data supporting the results reported in the article can be found including, where applicable, hyperlinks to publicly archived datasets analysed or generated during the study.

Data availability statements can take one of the following forms (or a combination of more than one if required for multiple datasets):

- The datasets generated and/or analysed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- All data generated or analysed during this study are included in this published article [and its supplementary information files].

- The datasets generated and/or analysed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

- Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].

- Not applicable. If your manuscript does not contain any data, please state 'Not applicable' in this section.

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Hao Z, AghaKouchak A, Nakhjiri N, Farahmand A. Global integrated drought monitoring and prediction system (GIDMaPS) data sets. figshare. 2014. http://dx.doi.org/10.6084/m9.figshare.853801

b) Competing interests

If you do not have any competing interests, please state "The authors declare that they have no competing interests" in this section.

c) Funding

All sources of funding for the research reported should be declared. The role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

d) Authors' contributions

The individual contributions of authors to the manuscript should be specified in this section.

Please use initials to refer to each author's contribution in this section, for example: "FC analyzed and interpreted the patient data regarding the hematological disease and the transplant. RH performed the histological examination of the kidney and was a major contributor in writing the manuscript. All authors read and approved the final manuscript."

e) Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials.

Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

f) Authors' information

This section is optional.

You may choose to use this section to include any relevant information about the author(s) that may aid the reader's interpretation of the article, and understand the standpoint of the

author(s). This may include details about the authors' qualifications, current positions they hold at institutions or societies, or any other relevant background information. Please refer to authors using their initials. Note this section should not be used to describe any competing interests.

Endnotes

Endnotes should be designated within the text using a superscript lowercase letter and all notes (along with their corresponding letter) should be included in the Endnotes section. Please format this section in a paragraph rather than a list.

Web links and URLs: All web links and URLs, including links to the authors' own websites, should be given a reference number and included in the reference list rather than within the text of the manuscript. They should be provided in full, including both the title of the site and the URL, as well as the date the site was accessed, in the following format: The Mouse Tumor Biology Database. http://tumor.informatics.jax.org/mtbwi/index.do. Accessed 20 May 2013. If an author or group of authors can clearly be associated with a web link, such as for weblogs, then they should be included in the reference.

General formatting guidelines:

a) Preparing main manuscript text

- Use double line spacing
- Include line and page numbering

- Use SI units: Please ensure that all special characters used are embedded in the text, otherwise they will be lost during conversion to PDF
- Do not use page breaks in your manuscript

b) File formats

The following word processor file formats are acceptable for the main manuscript document:

- Microsoft word (DOC, DOCX)
- Rich text format (RTF)
- TeX/LaTeX (use BioMed Central's TeX template)
- Please note: editable files are required for processing in production. If your manuscript contains any non-editable files (such as PDFs) you will be required to re-submit an editable file when you submit your revised manuscript, or after editorial acceptance in case no revision is necessary.
- Note that figures must be submitted as separate image files, not as part of the submitted manuscript file. For more information, see Preparing figures below.

c) Preparing figures

When preparing figures, please follow the formatting instructions below.

- Figures should be provided as separate files, not embedded in the main manuscript file.
- Each figure of a manuscript should be submitted as a single file that fits on a single page in portrait format.

- Tables should NOT be submitted as figures but should be included in the main manuscript file.
- Multi-panel figures (those with parts a, b, c, d etc.) should be submitted as a single composite file that contains all parts of the figure.
- Figures should be numbered in the order they are first mentioned in the text, and uploaded in this order.
- Figures should be uploaded in the correct orientation.
- Figure titles (max 15 words) and legends (max 300 words) should be provided in the main manuscript, not in the graphic file.
- Figure keys should be incorporated into the graphic, not into the legend of the figure.
- Each figure should be closely cropped to minimize the amount of white space surrounding the illustration. Cropping figures improves accuracy when placing the figure in combination with other elements when the accepted manuscript is prepared for publication on our site. For more information on individual figure file formats, see our detailed instructions.
- Individual figure files should not exceed 10 MB. If a suitable format is chosen, this file size is adequate for extremely high-quality figures.

Figure file types

We accept the following file formats for figures:

- EPS (suitable for diagrams and/or images)
- PDF (suitable for diagrams and/or images)
- Microsoft Word (suitable for diagrams and/or images, figures must be a single page)
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Figure size and resolution

Figures are resized during publication of the final full text and PDF versions to conform to the BioMed Central standard dimensions, which are detailed below.

Figures on the web:

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- width of 170 mm for full page width figure
- maximum height of 225 mm for figure and legend
- image resolution of approximately 300 dpi (dots per inch) at the final size

Figures should be designed such that all information, including text, is legible at these dimensions. All lines should be wider than 0.25 point when constrained to standard figure widths. All fonts must be embedded.

d) Preparing tables

When preparing tables, please follow the formatting instructions below.

- Tables should be numbered and cited in the text in sequence using Arabic numerals (i.e. Table 1, Table 2 etc.).
- Tables less than one A4 or Letter page in length can be placed in the appropriate location within the manuscript.

- Tables larger than one A4 or Letter page in length can be placed at the end of the document text file. Please cite and indicate where the table should appear at the relevant location in the text file so that the table can be added in the correct place during production.

- Larger datasets, or tables too wide for A4 or Letter landscape page can be uploaded as additional files. Please see [below] for more information.

- Tabular data provided as additional files can be uploaded as an Excel spreadsheet (.xls) or comma separated values (.csv). Please use the standard file extensions.

- Table titles (max 15 words) should be included above the table, and legends (max 300 words) should be included underneath the table.

- Tables should not be embedded as figures or spreadsheet files, but should be formatted using 'Table object' function in your word processing program.

- Color and shading may not be used. Parts of the table can be highlighted using superscript, numbering, lettering, symbols or bold text, the meaning of which should be explained in a table legend.

- Commas should not be used to indicate numerical values.

e) Preparing additional files

As the length and quantity of data is not restricted for many article types, authors can provide datasets, tables, movies, or other information as additional files.

All Additional files will be published along with the accepted article. Do not include files such as patient consent forms, certificates of language editing, or revised versions of the main manuscript document with tracked changes. Such files, if requested, should be sent by email to the journal's editorial email address, quoting the manuscript reference number. Please do not send completed patient consent forms unless requested.

Results that would otherwise be indicated as "data not shown" should be included as additional files. Since many web links and URLs rapidly become broken, BioMed Central requires that supporting data are included as additional files or deposited in a recognized repository. Please do not link to data on a personal/departmental website. Do not include any individual participant details. The maximum file size for additional files is 20 MB each, and files will be virus-scanned on submission. Each additional file should be cited in sequence within the main body of text.

If additional material is provided, please list the following information in a separate section of the manuscript text:

- File name (e.g. Additional file 1)
- File format including the correct file extension for example .pdf, .xls, .txt, .pptx (including name and a URL of an appropriate viewer if format is unusual)
- Title of data
- Description of data

Additional files should be named "Additional file 1" and so on and should be referenced explicitly by file name within the body of the article, e.g. 'An additional movie file shows this in more detail [see Additional file 1]'.

Items within additional files can be referenced in the main manuscript. However, please use the format set out in the following example: “See Supplementary Table 1, Additional File 1”

Appendix 2

Protocol:

Prevalence of non-communicable diseases in adults living with Human Immunodeficiency Virus: An Overview of Systematic Reviews.

Principal investigator: Shahista Mustafa Jaffer

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Abbreviations and keywords

Abbreviations:

NCD's – Non-communicable diseases

PLHIV – People living with HIV

HIV – Human immunodeficiency virus

AIDS – Acquired immunodeficiency syndrome

ART – Antiretroviral Therapy

DSM 5 - Diagnostic and Statistical Manual of Mental Disorders Fifth Edition

FBG – Fasting Blood Glucose

RBG - Random Blood Glucose

OGTT - Oral Glucose Tolerance Test

HbA1c - Glycated Hemoglobin

LDL – Low Density Lipoproteins

HDL - High Density Lipoproteins

Keywords – Non-communicable diseases, People living with HIV, Human immunodeficiency virus, Antiretroviral Therapy

Introduction

Background

Human immunodeficiency virus (HIV) and Acquired immunodeficiency syndrome (AIDS) is a very well-known and well researched infectious disease. The global prevalence of HIV has been noted to have increased from 33.3 million people in 2010 to 36.7 million people on average by the end of 20151.

Over the years, the use of combined Antiretroviral Therapy (ART) has reduced mortality from the disease despite it being incurable such that deaths from AIDS reduced from 1.5million in 2010 to 1.1 million by the end of 20151. Also, life expectancy has increased due to the several mechanisms through which ART suppress viral replication, reduce the occurrence of opportunistic infections and improve immune function. It has been documented that the use of ART has led to a stability in the acquisition of new HIV infections amongst all ages such that the number of new infections dropped by a million people from 2.3 to 2.1 million in 2010 and 2015 respectively1. This may aid the UNAIDS to achieve their 90-90-90 goal of ending the AIDS epidemic.

However, with increased life expectancy, aging is inevitable and thus the diseases associated with aging such as cardiovascular abnormalities, hypertension, insulin resistance/diabetes mellitus, cholesterol abnormalities, neurodegenerative disorders and so forth occur. Research suggests the emergence of such diseases much earlier in the HIV population than seen in the general population. For instance, a study in the US in 2010 showed that older HIV patients had a higher prevalence of hypertension 54%, hypertriglyceridemia 51% and low bone mineral density 39% compared to the general population of the same age 38%, 33% and 0% respectively 2. Another study done in Brazil suggested that there is premature aging in people living with HIV (PLHIV) by 15 years and that HIV is diagnosed at an early age between 18-39years 3 leading to increased ART use in the older population and increasing the incidence of non-communicable diseases (NCD's) such as hypertension, dyslipidemia, diabetes mellitus, obesity and depression with older age 3, 4, 5 due to prolonged exposure to ART.

Aging is not the only mechanism leading to the development of these NCD's, these findings can be attributed to the disease process itself via its viral properties or the inflammation and reaction by the human body, and to the toxic effects of the ART which leads to ART induced endothelial dysfunction as shown by a systematic review done by Nduka CU et al 6. Also, studies reveal that the number of years since the diagnosis of HIV and the duration and type of ART received is crucial in the development of NCD's. A study done in Mwanza region of Tanzania in 2013 showed that PLHIV on ART for more than 2 years had a prevalence of 28.7% for hypertension while those naïve to ART had a prevalence of 5.3% 7.

Another important aspect of the ART is the type of ART in question, it has been shown that people receiving a combination of Zidovudine/Lamivudine/Nevirapine (1st line treatment) are at an increased risk of hypertension while those receiving the non-standard 1st line treatment or the 2nd line drugs are at increased risk of Diabetes8. Long duration of ART and the use of protease inhibitors are also associated with increased risk of metabolic syndrome9. These findings are from clinical trials hence we may need more trials to certainly see the same effects in other populations.

With a slow progress in the decline of new HIV infections amongst adults10, it has become a chronic problem and is being more associated with NCD's at younger ages than in the general population. A huge burden of HIV of about 71% lies in the Sub-Saharan Africa (SSA) which is home to only about 12% of the global population11 with marked ART coverage over the last few years in different countries within the SSA10 as we aim to reach the 90-90-90 target set by the UNAIDS thus putting patients at the risk of developing NCD's earlier indefinitely.

Why is it important to do this review?

There have been many systematic reviews done on the prevalence of comorbidities in patients with HIV such as Type II diabetes mellitus, hypertension, dyslipidemia, neurological degeneration, chronic kidney diseases and thus we aim to consolidate all the available information in order to summarize the prevalence of co- and multi-morbidity in PLHIV and provide information to health institutions for planning of healthcare services for these patients in order to detect and treat early. Also, new studies need to be informed by the existing body of research.

Objectives

The aim of this overview is to determine the prevalence of one or more NCD's - diabetes mellitus type 2, hypertension, dyslipidemia and depression – in adults with HIV on ART.

Methods

Definitions

Multimorbidity is defined as the existence of two or more chronic medical conditions in a person that reduces his quality of life and functional abilities leading to increased hospital visits12. Thus, the presence of HIV along with two or more NCD's will be described as multimorbidity while the presence of one chronic disease in a patient with HIV will be described as comorbidity.

Diabetes mellitus type 2 is a chronic disease which is characterized by hyperglycemia/ raised blood sugar due to the body's inability to effectively utilize insulin. Uncontrolled diabetes over time may lead to severe damage especially to the nerves and blood vessels. The diagnosis of diabetes us usually made by doing blood tests such as raised fasting blood

glucose (FBG) > 7mmol/L, random blood glucose of > 11.1mmol/L, glycated hemoglobin (HbA1c) > 6.5mmol/L or a two-hour oral glucose tolerance test (OGTT) of > 11.1mmol/L13.

Hypertension is defined as persistently raised systolic and/or diastolic blood pressures of >140mmHg and >90mmHg respectively. Also, patients who are using any antihypertensive/ blood pressure lowering medicine suffer from hypertension14.

Depression is part of a range of depressive disorders which are characterized by the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function. The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5TM) has grouped the following under depressive disorders: disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, and depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder15.

Dyslipidemia is defined as elevated total serum cholesterol of > 5mmol/L or elevated low-density lipoproteins (LDL) of > 3mmol/L or raised Triglycerides > 1.7mmol/L or low levels of high-density lipoproteins (HDL) < 1.2mmol/L. Self-reporting use of lipid lowering drugs can also be used to confirm the diagnosis16.

Criteria for Considering Systematic Reviews for Inclusion

Types of reviews and studies

All systematic reviews determining the prevalence of NCD’s using cross-sectional studies in PLHIV. We will also review protocols for systematic reviews and if the reports are available

prior to submitting this overview, we will also include those results in our study. Systematic reviews are defined as studies that answer a research question by collecting and summarizing all empirical evidence that fits pre-specified eligibility criteria. It must have its objectives stated a priori and should have searched for studies on two or more databases including grey literature/unpublished work. Extracted data should have been analyzed, and a risk of bias assessed for each study with results presented appropriately17.

Types of participants

All adults above 18 years of age with HIV on treatment with any regimen of ART. We will not include pregnant women.

Types of outcomes

Primary outcomes

Prevalence of two or more NCD's namely diabetes mellitus, hypertension, dyslipidemia and depression in adults with HIV on ART.

Secondary outcomes

1. Prevalence of individual NCD's specifically diabetes mellitus, hypertension, dyslipidemia and depression in adults with HIV on ART.

2. Distribution of these NCD's according to demographics such as age, gender, duration and type of ART.

Search Methods for Identification of Systematic Reviews

We will search for existing systematic reviews in the Cochrane library, Medline, EMBASE, EBSCO host and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). For ongoing systematic reviews, we will search in Prospero. There will be no restrictions on language.

Key words that will be used to conduct our search include “non-communicable diseases”; "Human immunodeficiency virus” OR “HIV”; "Antiretroviral therapy” OR “ART”; “Review” OR “Systematic review”; “Type 2 diabetes mellitus” OR “Diabetes mellitus” OR “Adult onset diabetes mellitus”; “Hypertension” OR “High blood pressure” OR “Raised blood pressure”; “Depression“ OR “Major depressive disorder” OR “MDD” OR “Depressive disorder” and “Dyslipidemia” OR “Hypercholesterolemia” OR “High blood cholesterol”.

Systematic Review Selection, Data Collection, Quality Assessment and Analysis

Selection of reviews

Two authors will independently assess the eligibility of the reviews obtained from the electronic search. They will first screen through the titles and abstracts to determine potentially eligible articles. They will then obtain full texts of the relevant articles and apply the pre-specified eligibility criteria in order to be able to include them in the overview. Any discrepancy in the selection of studies will be resolved by discussion.

Data extraction and management

Data will be extracted from the eligible systematic reviews by two authors independently into a predesigned and piloted data extraction form. Data that will be extracted from the reviews include:

- Characteristics of the systematic reviews including the study designs and their objectives.
- Participants' characteristics including age groups, gender and types/classes of ART's being used.
- Setting
- Results of the studies i.e. the prevalence of each type of NCD assessed and the prevalence of two or more NCD's in PLHIV.

Data will be summarized in characteristics of included review tables. Overlap between reviews will also be examined by preparing a matrix detailing reviews and studies included in the reviews.

Assessment of methodological quality of included systematic reviews

We will assess the methodological quality of each of the included systematic reviews using the AMSTAR 2 tool18 which is a revision of the AMSTAR tool in order to identify high quality

Systematic reviews. AMSTAR 2 is a critical appraisal tool for systematic reviews that include randomized or non-randomized studies of health care interventions. It consists of 16 domains which must be answered with a yes, partial yes or a no18.

We will not answer all the domains of the AMSTAR 2 tool as they focus on intervention studies while this overview focuses on systematic reviews of prevalence studies, thus we will use the domains that are applicable to appraising the quality of systematic reviews in general. We will not generate an overall score for each systematic review, rather we will consider the potential impact of an inadequate rating for each item.

If there are any discrepancies in the data extracted by the two authors from the systematic reviews, then we will try to obtain the original article that was included in the systematic review and review its findings. Any disagreements between the authors will be solved by discussion.

Data syntheses and analysis

Because of the nature of the primary studies involved i.e. descriptive studies, we will provide a narrative summary of our findings considering all the participants, their NCD and ART status. Therefore, we plan to report on the prevalence of each type of NCD identified as well as the prevalence of two or more NCD's in PLHIV with its 95% confidence interval. This will give us an overview of the challenge that the health care system faces whilst caring for HIV patients who also have other chronic diseases.

Results

Description of included reviews

Quality of included reviews (AMSTAR)

Findings after combining the reviews

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